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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,970	01/16/2004	Michael Tyo	08191-012002	6224

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EXAMINER	
POPA, ILEANA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 12/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

TH

Office Action Summary	Application No.	Applicant(s)	
	10/758,970	TYO ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of the species of diluting in the reply filed on 10/05/2006 is acknowledged. However, upon further consideration the requirement for species election is withdrawn.

Claims 1-47 are pending and under examination.

Claim Objections

2. Claim 32 is objected to because of the following informalities: the instant claim already recites a range between about 0.5 and 2.5 μ and therefore, the use of the term "inclusive" is redundant. Appropriate correction is required.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-4, 12-17, 19-25, and 32-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shah (U.S. Patent No. 6,020,004), in view of both Chen et al. (U.S. Patent No. 6,537,813) and Tice et al. (U.S. Patent 4,389,330).

Shah teaches a continuous process for the preparation of 0.5 μ microparticles for nucleic acid delivery, the process comprising obtaining a first emulsion by mixing, in a homogenizer, PLGA dissolved in an organic solvent with a first aqueous solution of a nucleic acid, and mixing the first emulsion with a second aqueous solution comprising a surfactant, and a stabilizer comprising sucrose and a buffer such as Tris-HCl (i.e., both the first emulsion and the first aqueous solution comprise a stabilizer), and further mixing this combination to form a second emulsion, then transferring the second emulsion to a lyophilizer to remove the solvents (claims 1, 3, 17, 32-36, 41, and 42) (column 4, lines 25-65, column 5, lines 50-62, column 6, lines 5-45, column 7, lines 30-40, Example 1). Shah also teaches that the organic solvent comprises methylene chloride (i.e., dichloromethane) (claim 25) and that the second aqueous solution can comprise polyvinyl alcohol (claim 40) (column 6, lines 5-7, Example 1). Shah does not teach a scalable continuous process. Chen et al. teach a scaleable, concurrent flow mixing method and apparatus for the preparation of nucleic acid-containing microparticles, wherein the method comprises concurrently introducing and mixing at least a first molecular entity-containing solution and a second molecular entity-containing solution into a flow through mixer (i.e., mixer chamber) to form an uniform microparticle suspension, collecting the suspension in vessels attached to the apparatus, and storing the microparticles in solution or in more concentrated forms,

including lyophilized particles (column 1, lines 15-22, column 3 bridging column 4, column 19, lines 50-60). Chen et al. teach that their method and apparatus can be adapted for (i) the mixing of more than two solution, wherein the mixing of the first components takes place before the introduction of the additional solutions (column 9 bridging column 10) and (ii) a continuous process (column 21, lines 47-63). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Shah by using the apparatus of Chen et al., with a reasonable expectation of success. The motivation to do so is provided by Chen et al., who teach that no other mixing format allows for convenient, reliable, reproducible, and scaleable process that results in the production of uniform quality and particle size specific for different applications (column 6, bridging column 7, column 10 bridging column 11). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because Chen et al. teach that their apparatus can be successfully adapted for the preparation of microparticles with diverse composition, according to the needs.

Neither Shah, nor Chen et al. teach removing the organic solvent from the second emulsion to form an aqueous suspension of microcapsules (step "f" of claim 1). Tice et al. teach that removal of the organic solvent in two distinct steps, rather than in one step, results in microcapsules with improved quality and containing a higher level of active agent, wherein the first steps involves techniques common in the art such as evaporation, heating, extraction or vacuum (claims 20-22 and 24) followed by separation of the microcapsules from the fluid medium by filtration through a fine (4-5.5

μm) fritted-glass funnel and removal of the remaining solvent by resuspending the microcapsules in water, wherein the water extracts the solvent from the microcapsules (claim 23). Tice et al. teach that during the second extraction step, the aqueous medium with the extracted solvent must be removed and replaced with fresh aqueous medium on a continuous basis and that after the remaining of the solvent has been removed, the microcapsules are dried by conventional techniques (column 2, lines 14-29, column 4, lines 9-54, column 6, Example 1). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to further modify the method taught by the combined teachings of Shah and Chen et al. by removing the solvent using the two-step procedure of Tice et al., with a reasonable expectation of success. The motivation to do so is provided by Tice et al., who teach that the two-step procedure results in higher levels of active agent as compared with the conventional one-step procedure. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches this procedure can be successfully used to obtain better quality particles, while preserving the activity of the encapsulated agent.

With respect to the limitations recited in claims 19 and 44-46, Chen et al. teach that both the size and uniformity is regulated by controlling the mixing ratio, flow rate, and mixing rate (column 6 bridging column 7). Absent evidence of unexpected results, if the general conditions of a given method are disclosed in the prior art, it would have been obvious to the ordinary skilled artisan to vary the parameters in a given method with the purpose of optimizing the results. Again, absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method,

such conditions can be identified by routine experimentation.

With respect to the limitations of the buffer being Tris-EDTA (claim 4), the first and second solution having the same osmolarity (claim 2), of the wash solution being sterile water at a temperature of about 2°C to about 8°C (claim 14), of adding an excipient (claim 15), transferring the dried microparticles into one or more vessels (claim 16), of the heating between 30°C and 55°C (claim 21), of the ratio of lactic acid to glycolic acid being between about 1:2 and about 4:1 (claim 37) or about 1:1 (claim 38), of the PLGA having an average molecular weight of 6,000 to 100,000 (claim 39), or of the emulsifying step being carried out between about 2°C to about 8°C (claim 43), absent evidence of unexpected results, if the general conditions of a given method are disclosed in the prior art, it would have been obvious to the ordinary skilled artisan to vary the parameters in a given method with the purpose of optimizing the results. One of skill in the art would have discovered the optimal working conditions by routine experimentation.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

5. Claims 1-6, 12-17, 19-25, and 32-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shah taken with Chen et al. and Tice et al., as applied to claims 1-4, 12-17, 19-25, and 32-46 above, in further view of Parikh et al. (U.S. Patent No. 5,660,858).

Shah taken with Chen et al. and Tice et al. do not teach a lipid as a stabilizer (claims 5 and 6). Parikh et al. teach using lipids as stabilizers. It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Shah taken with Chen et al. and Tice et al. by including lipid stabilizers, with a reasonable expectation of success. The motivation to do so is provided by Parikh et al., who teach that the use of lipids results in increased stability during diverse processing steps, such as heating or storage, and also under stress conditions, such as shaking, vibrating, and termal cycling (column 3, lines 2-6). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that lipids can be successfully incorporated into microparticles. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

6. Claims 1-4, 7-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shah taken with Chen et al. and Tice et al., as applied to claims 1-4, 12-17, 19-25, and 32-46 above, in further view of both Hartounian et al. (PGPUB 2002/0039596) and Hedley et al. (U.S. Patent 5,783,567).

Shah taken with Chen et al. and Tice et al. do not teach a diafiltration apparatus. Hartounian et al. teach aseptical preparation of liposomes using a diafiltration apparatus such as a hollow fiber filter (i.e., a bioreactor) (p. 2, paragraphs 0020 and 0021, p. 4, paragraph 0062, p. 5, paragraphs 0063-0066, p. 9, paragraphs 0112, p. 10, paragraph 0126). It would have been obvious to one of skill in the art, at the time the invention

was made, to optimize the production process by employing diafiltration apparatuses, as taught by Hartounian et al. One of ordinary skill in the art would have been motivated to do so in order to enhance the production of large quantities of microparticles for use in the delivery of nucleic acids and to reduce the time in preparing the desired amount of particles. Since the totality of the prior art of record teaches that the microparticles are for *in vivo* use, one of ordinary skill in the art would have been motivated to ensure that all of the components used in the making of the microparticles are sterile, so as to ensure that sterility is preserved throughout the process. One of skill in the art would have been expected to have a reasonable expectation of success in doing so because the art teaches that such methods can be successfully practiced. With respect to the different residual organic solvent levels recited in claims 10 and 11, Shah teaches that the removal of organic solvent during lyophilization can be monitored (Example 1); therefore, one of skill in the art would only require routine experimentation to achieve and determine these levels. With respect to the limitations of the nucleic acid being in the form of circular RNA or supercoiled DNA (claims 29-31), one of ordinary skill in the art would have expected that either circular RNA or supercoiled DNA molecules are present in the microparticles, because the conditions of encapsulating nucleic acids within micreoparticles without destroying their structure, thereby allowing for the intracellular delivery of functional RNA or DNA via microparticles, were routine at the time the invention was made, (see Hedley et al., Abstract, column 1, lines 30-58). Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

7. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

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AU1633